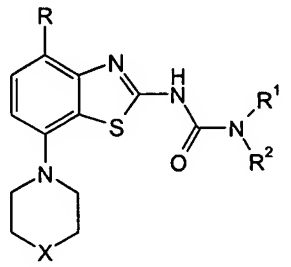
Claims

1. A method of treatment of diseases responsive to modulation of the adenosine A_2 receptor comprising administering a therapeutically effective amount of a compound of formula



I

wherein

R is lower alkoxy or halogen;

R^1/R^2 are independently selected from the group consisting of hydrogen, lower alkyl, cycloalkyl,

tetrahydropyran-4-yl,

or R^1 and R^2,together with the N atom to which they are attached, form a heterocyclic ring, selected from the group consisting of

2-oxa-5-aza-bicyclo[2.2.1]heptane,

3-endo-hydroxy-8-aza-bicyclo[3.2.1]octane,

2-aza-bicyclo[2.2.2]octane,

1-oxo-2,8-diaza-spiro[4.5]decane,

3-aza-spiro[5.5]undecane,

8-aza-spiro[4.5]decane,

1-oxa-8-aza-spiro[4.5]decane,

1,8,8-trimethyl-3-aza-bicyclo[3.2.1]octane,

[1,4]oxazepane,

2-oxa-5-aza-bicyclo[2.2.2]octane,

8-oxa-3-aza-bicyclo[3.2.1]octane,

1,4-diaza-bicyclo[3.2.1]octane,

2-aza-bicyclo[2.2.1]heptane

3-aza-bicyclo[3.2.1]octane, said heterocylic ring being unsubstituted or substituted by lower alkyl, or

piperazinyl, said piperazlinyl being unsubstituted or being substituted by one or two substituents selected from lower alkyl, phenyl and oxo, or

piperidin-1-yl substituted by $-(CH_2)_n$-NR'S(O)$_2$-lower alkyl, -C(O)NR'$_2$ and $-(CH_2)_n$-phenyl, said phenyl ring being unsubstituted or substituted by lower alkyl, and wherein R' is independently selected from hydrogen and lower alkyl;

X is –O- or $-CH_2$; and

n is 0, 1, 2, 3 or 4

or a pharmaceutically acceptable acid addition salt thereof to a person in need of such treatment.

2. The method of treatment of claim 1, wherein the disease being treated is selected from Alzheimer's disease, Parkinson's disease, Huntington's disease, neuroprotection, schizophrenia, anxiety, pain, respiration deficits, depression, drug addiction, asthma, allergic responses, hypoxia, ischaemia, seizure substance abuse, coronary artery disease and heart failure.

3. The method of treatment according to claim 2, wherein X is –O-.

4. The method of treatment according to claim 3, wherein the compound is selected from the group consisting of

(1*S*,4*S*)-2-oxa-5-aza-bicyclo[2.2.1]heptane-5-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide,

3-*endo*-hydroxy-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide,

2-methyl-1-oxo-2,8-diaza-spiro[4.5]decane-8-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide,

1-oxo-2,8-diaza-spiro[4.5]decane-8-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide,

4-benzyl-4-hydroxymethyl-piperidine-1-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide,

3-aza-spiro[5.5]undecane-3-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide,

8-aza-spiro[4.5]decane-8-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-

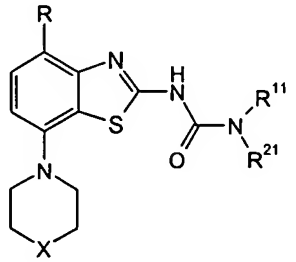
amide,
2-aza-bicyclo[2.2.2]octane-2-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide,
1-oxa-8-aza-spiro[4.5]decane-8-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide,
(*R*)-4-(1-hydroxy-ethyl)-piperidine-1-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide,
(*S*)-4-(1-hydroxy-ethyl)-piperidine-1-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide,
4-(methanesulfonylamino-methyl)-piperidine-1-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide,
piperidine-1,4-dicarboxylic acid 4-amide 1-[(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide],
1-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-3-(tetrahydro-pyran-4-yl)-urea,
4-isopropyl-piperazine-1-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide,
4-phenyl-piperazine-1-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide,
1-cyclohexyl-3-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-1-methyl-urea,
1-(4*cis*-fluoro-cyclohexyl)-3-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-1-methyl-urea,
1-(4*cis*-fluoro-cyclohexyl)-3-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-1-methyl-urea,
(*cis*)-1-(4-methoxy-cyclohexyl)-3-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-1-methyl-urea,
(*trans*)-1-(4-hydroxy-cyclohexyl)-3-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-1-methyl-urea,
[1,4]oxazepane-4-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide,
(*cis*)-1-(4-hydroxy-cyclohexyl)-3-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-1-methyl-urea,
2-oxa-5-aza-bicyclo[2.2.2]octane-5-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide,
(*trans*)-1-(4-methoxy-cyclohexyl)-3-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-1-methyl-urea,
(1S,4R)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid (4-methoxy-7-morpholin-4-yl-

benzothiazol-2-yl)-amide,
3-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-1-methyl-1-(tetrahydro-pyran-4-yl)-urea,
1-cycloheptyl-3-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-1-methyl-urea,
1-cyclopentyl-3-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-1-methyl-urea and
1-cyclopentyl-3-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-urea.

5. The method of treatment according to claim 2, wherein X is $-CH_2-$.

6. The method of treatment according to claim 5, wherein the compound is selected from the group consisting of
1-oxa-8-aza-spiro[4.5]decane-8-carboxylic acid (4-methoxy-7-piperidin-1yl-benzothiazol-2-yl)-amide,
4-hydroxy-4-(4-methyl-benzyl)-piperidine-1-carboxylic acid (4-chloro-7-piperidin-1-yl-benzothiazol-2-yl)-amide,
4-benzyl-piperidine-1-carboxylic acid (4-chloro-7-piperidin-1-yl-benzothiazol-2-yl)-amide,
4-methyl-3-oxo-piperazine-1-carboxylic acid (4-methoxy-7-piperidin-1-yl-benzothiazol-2-yl)-amide and
1-(4-chloro-7-piperidin-1-yl-benzothiazol-2-yl)-3-cyclohexyl-urea.

7. A compound of formula



IA

wherein
R is lower alkoxy or halogen;
R^{11} and R^2, together with the N atom to which they are attached, form a heterocyclic ring, said heterocyclic ring being unsubstituted or substituted by lower alkyl, selected from the group consisting of
2-oxa-5-aza-bicyclo[2.2.1]heptane,
3-endo-hydroxy-8-aza-bicyclo[3.2.1]octane,

2-aza-bicyclo[2.2.2]octane,
1-oxo-2,8-diaza-spiro[4.5]decane,
3-aza-spiro[5.5]undecane,
8-aza-spiro[4.5]decane,
1-oxa-8-aza-spiro[4.5]decane,
1,8,8-trimethyl-3-aza-bicyclo[3.2.1]octane,
[1,4]oxazepane,
2-oxa-5-aza-bicyclo[2.2.2]octane,
8-oxa-3-aza-bicyclo[3.2.1]octane,
1,4-diaza-bicyclo[3.2.1]octane,
2-aza-bicyclo[2.2.1]heptane and
3-aza-bicyclo[3.2.1]octane, or
piperidin-1-yl, substituted by a substituent selected from the group $-(CH_2)_n$-NR'$S(O)_2$-lower alkyl, -C(O)NR'$_2$ and $-(CH_2)_n$-phenyl, said phenyl ring being unsubstituted or substituted by lower alkyl, and R' being independently selected from hydrogen and lower alkyl;

X is $-CH_2$-; and

n is 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable acid addition salt thereof.

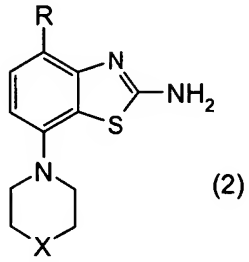
8. The compound of formula IA according to claim 7, wherein the compound is selected from the group consisting of

1-oxa-8-aza-spiro[4.5]decane-8-carboxylic acid (4-methoxy-7-piperidin-1yl-benzothiazol-2-yl)-amide,

4-hydroxy-4-(4-methyl-benzyl)-piperidine-1-carboxylic acid (4-chloro-7-piperidin-1-yl-benzothiazol-2-yl)-amide and

4-benzyl-piperidine-1-carboxylic acid (4-chloro-7-piperidin-1-yl-benzothiazol-2-yl)-amide.

9. A process for preparing a compound of formula IA as defined in claim 7 comprising reacting a compound of formula

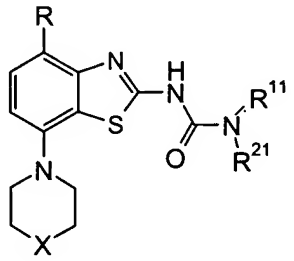


(2)

with phenyl chloroformate and then with a compound of formula

$$HNR^{11}R^{21} \quad (3A)$$

forming a compound of formula

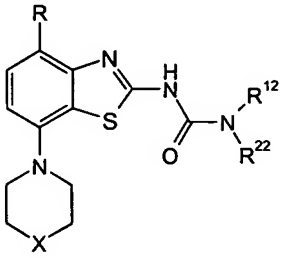


IA

10. A pharmaceutical composition comprising a compound of formula IA according to claim 7, or a pharmaceutically acceptable salt thereof; and a pharmaceutically inert carrier.

11. A method of neuroprotection and treating Alzheimer's disease, depressive disorders, drug addiction, Parkinson's disease and ADHD comprising administering a therapeutically effective amount of a compound of formula IA, or a pharmaceutically acceptable salt thereof, according to claim 7 to a person in need of such treatment.

12. A compound of formula



IB

wherein

R is lower alkoxy or halogen;

R^{12} is lower alkyl and

R^{22} is cycloalkyl, substituted by one or two substituents, selected from the group consisting of halogen, lower alkoxy or hydroxy; and

X is –O- or CH_2-;

or a pharmaceutically acceptable acid addition salt thereof.

13. The compound of formula IB according to claim 12, wherein X is –O-.

14. The compound of formula IB according to claim 13, wherein the compound is selected from the group consisting of

1-(4*cis*-fluoro-cyclohexyl)-3-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-1-methyl-urea,

1-(4,4-difluoro-cyclohexyl)-3-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-1-methyl-urea,

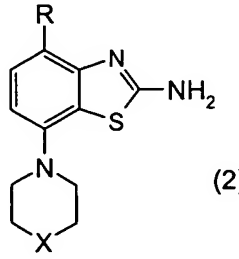
(*cis*)-1-(4-methoxy-cyclohexyl)-3-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-1-methyl-urea,

(*trans*)-1-(4-hydroxy-cyclohexyl)-3-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-1-methyl-urea,

(*cis*)-1-(4-hydroxy-cyclohexyl)-3-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-1-methyl-urea and

(*trans*)-1-(4-methoxy-cyclohexyl)-3-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-1-methyl-urea.

15. A process for preparing a compound of formula IB comprising reaction of a compound of formula

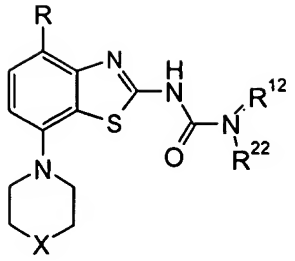


(2)

with phenyl chloroformate and then with a compound of formula

$HNR^{12}R^{22}$ (3B)

forming a compound of formula



IB

wherein R is lower alkoxy or halogen;

X is –O- or CH_2-;

R^{12} is alkyl; and

R^{22} is cycloalkyl, substituted by one or two substituents selected from the group consisting of halogen, lower alkoxy and hydroxy.

16. A pharmaceutical composition comprising a compound of formula IB according to claim 12 or a pharmaceutically acceptable salt thereof and a pharmaceutically inert carrier.

17. A method of neuroprotection and treating Alzheimer's disease, depressive disorders, drug addiction, Parkinson's disease and ADHD comprising administering a therapeutically effective amount of a compound of formula IB, or a pharmaceutically acceptable salt thereof, according to claim 12 to a person in need of such treatment.

18. A pharmaceutical composition comprising a compound of formula I according to claim 1, or a pharmaceutically acceptable salt thereof; and a pharmaceutically inert carrier.